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**Development and Evaluation of the**

**All Ages Lead Model (AALM)**

National Center for Environmental Assessment

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# EXECUTIVE SUMMARY

EPA’s Office of Research and Development (ORD) / National Center for Environmental Assessment (NCEA) is developing an All Ages Lead Model (AALM) that has the capability of predicting lead (Pb) concentrations in body tissues (e.g., blood, bone, brain) and excreta at any age resulting from acute or chronic exposures to Pb in environmental media. The AALM represents additional exposure modelling capability for regulatory use beyond previously developed models such as the Integrated Exposure Uptake Biokinetics (IEUBK) Model for Lead in Children, and the Adult Lead Methodology (ALM). The AALM offers considerable new capabilities and benefits, however, additional internal and external evaluation is needed, such that for the near term, the IEUBK and ALM models will remain the standard for regulatory use.

As a brief historical chronology of the AALM, development began in 1999 followed by an EPA Science Advisory Board (SAB) review in October 2005 of then version 1.05 of the AALM. The SAB highlighted the need for expanded documentation and further evaluation of the model, identified a number of deficiencies, and suggested potential improvements. Documentation was subsequently expanded and further detailed the improvements to be made, however, further development was hampered by problems and expense with configuration management, software updates requiring extensive revisions, and availability of sufficient expertise and familiarity with the complexity of the model. A re-invigorated effort starting in early 2013 successfully resulted in a considerably expanded AALM capability that remedied the key deficiencies identified by the SAB, added many new features, and incorporated updated extant data on Pb kinetics. Six major objectives have been realized in this most recent effort as described in this report including: (1) recoding of the AALM biokinetics models from Visual C to the more robust kinetic model development software, Advance Continuous Simulation Language, ACSL® (acslX); (2) addition of a user friendly, flexible, and transparent exposure model interface implemented in Microsoft Excel®(Excel); (3) capability to run either the Leggett (AALM-LG) or O’Flaherty (AALM-OF) biokinetics models from the same exposure model interface, and with the same exposure and absorption conditions; (4) a more realistic respiratory tract model representation in both the Leggett and O’Flaherty biokinetics models compared with earlier versions; (5) accessible and transparent output for easy comparison of the predictions from the Leggett and O’Flaherty biokinetics models; and (6) an evaluation and optimization of the Leggett and O’Flaherty biokinetics models against a common set of observations. Of particular interest to risk assessment applications are predictions of blood and bone Pb, as these two biomarkers have been used extensively to establish the dose-response relationships for health effects in humans following exposure to Pb. The AALM provides output for both of these compartments.

The current version of the AALM has introduced several changes to both the Leggett and O’Flaherty biokinetics models including some new parameters, and overall optimized parameter values against the same data sets. Some of these data used in the optimization were not available at the time the original models were developed. Optimization against a common set of data resulted in general convergence of AALM-LG and AALM-OF predictions for blood, bone, and soft tissue. For adults (ages >16), the optimized models predict long-term accrual of Pb, and blood and bone Pb levels that differ by less than 20%. The two models also predict similar blood Pb concentrations in children. At an earlier age of 2 years, however, blood Pb concentrations predicted from AALM-LG are approximately 25% lower than predictions from AALM-OF.

The initial set of optimized parameters for the AALM resulted in predictions of blood Pb concentrations in children that were approximately 2-fold higher than the IEUBK model. Data available for optimizing and evaluating performance of the Pb biokinetics models are largely limited to data for Pb kinetics in adults. Only two studies have reported data on intake-blood Pb relationships in infants ([Ryu et al. 1983](#_ENREF_48); [Sherlock and Quinn 1986](#_ENREF_50)), and no data of this type are available for children in the age range 1-7 years, the age range simulated in the IEUBK model. Given the large uncertainties in the available data on intake-blood Pb relationships in children, the model differences in absolute terms are relatively small in the context of model capabilities (e.g., approximately 1 - 2 µg/dL in children for a dust Pb ingestion rate of 10 µg/day). These small differences in model estimates, however, could have disproportionate costs implications to consider in making risk management decisions at contaminate sites, which are typically based on a “not-to-exceed” blood Pb concentration (U.S. EPA [1994](#_ENREF_57)). Thus, it was deemed worthwhile to further evaluate the most sensitive AALM parameter values to determine which parameters values could be calibrated against the IEUBK model output for child blood Pb concentrations relative to Pb intake without altering the AALM model performance in simulating the infant and adult data.

The additional evaluation identified value changes for a single biokinetic parameter controlling red blood cell Pb concentrations that were sufficient to align the AALM results more closely with the IEUBK model results for children without adversely impacting the good model agreement and predictive capability for infants or adults. There is good rationale for the adjustments to the red blood cell parameter as discussed in the report in Section 9, however, additional evaluations and data are likely to improve model performance and resolve remaining differences among the AALM-LG, AALM-OF, and IEUBK model results. Types of data most needed to support model parameter values and predictive accuracy include: (1) blood soft tissue or bone Pb levels in children or adults for whom Pb dosage is known or can be reliable estimated from exposure data; (2) changes in blood, soft tissue or bone Pb levels in children or adults following an abrupt change (increase or decrease) in Pb exposure; (3) steady state (or quasi-steady state) blood/soft tissue blood/bone Pb ratios in children or adults; (4) urinary Pb clearance from blood or plasma in children or adults; and (5) plasma/whole blood concentration ratios in children.

The AALM has great utility for regulatory use, a vastly more flexible and transparent exposure interface, and ready access to model parameters and code. The agreement between the AALM, the IEUBK model, and the ALM supports the potential future use of the AALM in risk assessment applications to supplement or replace the IEUBK model and the ALM in supporting regulatory decisions. Additional internal and external review, however, is needed, and the IEUBK model and the ALM will remain the established methods for Agency use in making regulatory decisions. We do recommend that the AALM be released as a beta test version for internal and external use to facilitate the development of additional case studies, needed data, and further evaluation and improvements.

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# ACRONYMS AND ABBREVIATIONS

AALM All Ages Lead Model

AALM-LG All Ages Lead Model-Leggett

AALM-OF All Ages Lead Model-O’Flaherty

ACSL Advance Continuous Simulation Language

ALM Adult Lead Methodology

GFR Glomerular filtration rate

HRTM Human Respiratory Tract Model

ICRP International Commission on Radiological Protection

IEUBK Integrated Exposure Uptake Biokinetics

NCEA National Center for Environmental Assessment

Pb Lead

RBA Relative bioavailability

SAB Science Advisory Board

SSCs Sensitivity analyses coefficients

U.S. EPA U.S. Environmental Protection Agency

XRF X-ray Fluorescence

# 1.0 INTRODUCTION

EPA’s Office of Research and Development (ORD) / National Center for Environmental Assessment (NCEA) is developing an All Ages Lead Model (AALM) that has the capability of predicting lead (Pb) concentrations in body tissues (e.g., blood, bone, brain) and excreta at any age resulting from acute or chronic exposures to Pb in environmental media. The AALM extends the capability of models previously developed by EPA such as the Integrated Exposure Uptake Biokinetics (IEUBK) Model for Lead in Children, and the Adult Lead Methodology (ALM). The IEUBK model simulates quasi-steady state exposure-blood lead concentration relationships occurring from birth to age 7 years ([Hogan et al. 1998](#_ENREF_16); [White et al. 1998](#_ENREF_59); [Zaragoza and Hogan 1998](#_ENREF_60)). The ALM simulates quasi-steady state exposure-blood lead concentration relationships in adults ([Maddaloni et al. 2005](#_ENREF_29)).

This report summarizes recent developments in the AALM that were initiated in early 2013. Six major objectives have been realized in this most recent effort, and are described in this report including: (1) recoding of the AALM biokinetics models from Visual C to the more robust kinetic model development software, Advance Continuous Simulation Language, ACSL® (acslX(); (2) addition of a user friendly, flexible, and transparent exposure model interface implemented in Microsoft Excel®(Excel); (3) capability to run either the Leggett (AALM-LG) or O’Flaherty (AALM-OF) biokinetics models from the same exposure model interface, and with the same exposure and absorption conditions; (4) a more realistic respiratory tract model representation in both the Leggett and O’Flaherty biokinetics models compared with earlier versions; (5) accessible and transparent output for easy comparison of the predictions from the Leggett and O’Flaherty biokinetics models; and (6) an evaluation and optimization of the Leggett and O’Flaherty biokinetics models against a common set of observations.

Section 2 provides a brief overview of the history of the development of the model and structure of the AALM. Section 3 compares the structures of the two biokinetics models contained in the AALM (AALM-LG, AALM-OF). Section 4 describes the outcomes of model runs that compare predictions of blood and tissue Pb levels obtained from the AALM-LG and AALM-OF. Section 5 presents the results of sensitivity analyses coefficients (SSCs) conducted from the AALM biokinetics models. Section 6 presents the conclusions from the model comparison. Section 7 presents results of an empirical evaluation and optimization of the AALM-LG and AALM-OF. Section 8 provides conclusions and discusses implications of performance of the optimized models for model applications. Section 9 discusses differences between the AALM model output and the IEUBK model for similar exposures, identifies AALM model parameter changes that resolve the differences, and provides a rationale for changes in the parameter values. Section 10 outlines the next steps to be taken, and the data needed to further develop and evaluate the AALM.

# 2.0 MODEL OVERVIEW

## 2.1 History of the AALM

In 1994, EPA’s Superfund Office released the IEUBK model version 0.99d and supporting documentation of the model for regulatory use in the EPA Superfund program (U.S. EPA [1994](#_ENREF_57)). The IEUBK model has been widely used at Superfund sites to develop remedial objectives. The IEUBK model simulates exposure and biokinetics of Pb from birth to age 7 years (84 months) and was developed for predicting average quasi-steady state blood Pb concentrations corresponding to daily average exposures, averaged over periods ≥1 year. The model has four major components or submodels:

* Exposure model, in which average daily intakes of Pb (μg/day, averaged over a 1-year time increment) are calculated for each inputted exposure concentration (or rates) of Pb in air, diet, dust, soil, and water;
* Uptake model, which converts environmental media-specific Pb intake rates calculated from the exposure model into a media-specific time-averaged rates of uptake (μg/day) of Pb to the central compartment (blood plasma);
* Biokinetic model, which simulates the transfer of absorbed Pb between blood and other body tissues, elimination of Pb from the body (via urine, feces, skin, hair, and nails), and predicts an average blood Pb concentration for the exposure time period of interest; and
* Blood Pb probability model, which simply applies a log-normal distribution (with specific geometric mean and geometric standard deviation parameters) to predict probabilities for the occurrence of a specified blood Pb concentration in a population of similarly exposed children.

Development of the AALM by EPA/ORD began in 1999 to extend Pb exposure and biokinetic modelling capability to all ages and smaller time frames (i.e., beyond the IEUBK Model and the ALM capability), and to address a wider range of model applications in computational Pb toxicology; these include:

* Simulation of Pb biokinetics associated with multimedia exposures occurring within any age range from fetal to age 90 years (the IEUBK model is limited to birth to age 84 months);
* Simulation of biokinetics of maternal-fetal transfer of Pb;
* Simulation of Pb biokinetics in blood, bone, soft tissues, and excreta (in the IEUBK model, Pb levels in tissues and excreta are intermediary variables used to support the blood Pb simulation, and are not output variables);
* Simulation of Pb biokinetics in response to changes in Pb exposure that occur over periods of days (the IEUBK model exposure averaging time is ≥1 year and predicts quasi-steady state blood Pb concentrations); and
* Expansion of the exposure model to include multiple sources of exposure from air, drinking water, food, and surface dust; historic exposure to Pb in air, drinking water, and food; and inputs of exposures to Pb in surface dust as Pb concentration in dust (µg Pb/g dust) or Pb loading (µg Pb/cm2 of surface).

Over the intervening years between initiation of the development of the IEUBK model in 1989 and its release for regulatory use in 1994, several modelling approaches were reported for simulating Pb biokinetics of life stages extending beyond earlier childhood. Two models in particular were influential in developing the structure of the AALM. The first was the Leggett model ([Leggett 1993](#_ENREF_27); [Pounds and Leggett 1998](#_ENREF_45)), based on a biokinetic model originally developed for the International Commission on Radiological Protection (ICRP) that calculated radiation doses from environmentally important bone-seeking radionuclides, including radioisotopes of Pb ([Leggett 1985](#_ENREF_24),[1992a](#_ENREF_25),[b](#_ENREF_26)). The original model was used to develop cancer risk coefficients for internal radiation exposures to Pb and other alkaline earth elements that have biokinetics similar to those of calcium (ICRP [1993](#_ENREF_19); U.S. EPA [1998](#_ENREF_56)). The compartment structure, Pb transfer coefficients, and numerical integration method of the Leggett model were adopted in the early versions of the AALM. The second model was the O’Flaherty model that simulates Pb exposure, uptake, and disposition in humans, from birth through adulthood ([O’Flaherty 1991a](#_ENREF_35),[b](#_ENREF_36),[c](#_ENREF_37), [1993](#_ENREF_38), [1995](#_ENREF_39), [1998](#_ENREF_40), [2000](#_ENREF_42)). Important features that distinguish the O’Flaherty model from the Leggett model are simulation of growth (the Leggett model simulates growth only of the blood volume), bone formation, and resorption (the Leggett model simulates the “effects” of bone growth and resorption of Pb kinetics, but does not simulate bone growth and resorption explicitly). Uptake and release of Pb from trabecular bone and metabolically active cortical bone are functions of bone formation and resorption rates, respectively, and are simulated in the O’Flaherty model; this establishes a relationship between the age dependence and the Pb kinetics in and out of bone, and allows for explicit simulation of the effects of bone formation (e.g., growth and loss, changes in bone volume, and bone maturation) on Pb uptake and release from bone. In contrast, the Leggett model represents age-dependence of bone Pb kinetics as age-dependent rate coefficients for transfer of Pb into and out of bone. Although the O’Flaherty model had a more physiologically accurate representation of bone growth and resorption, the Leggett model configuration for growth of the blood volume and bone Pb kinetics was also used for early versions of the AALM (up to 1.05).

In October of 2005, an EPA Science Advisory Board (SAB) reviewed version 1.05 (Visual C) of the AALM, and highlighted the need for expanded documentation and further evaluation of the model (U.S. EPA 2007). The SAB also identified a number of deficiencies, and suggested potential improvements. With additional technical support, EPA’s NCEA expanded the documentation and evaluation of the AALM to include the following: (1) a Guidance Manual for the AALM that describes the conceptual basis and structure of the model (including all equations, parameters, and parameter values) (SRC TR-08-142); (2) review and evaluation of evidence supporting further extension and/or refinement of the model (SRC TR-09-178); and (3) a comparative review of alternative modelling approaches (SRC TR-09-139). Although the documentation further detailed deficiencies and potential improvements that could be made to the AALM, further development was hampered by problems and expense with configuration management, maintaining software updates, and availability of sufficient expertise and familiarity with the complexity of the model.

As noted in the introduction, a re-invigorated effort initiated in early 2013 successfully resulted in a considerably expanded AALM capability that remedied the key deficiencies identified by the SAB, added many new features, and incorporated updated extant data on Pb kinetics. Utilizing acslX (or any other robust commercial simulation software) removed the need to develop and maintain computer code for the numerical integration solution of the AALM biokinetics model, and made use of existing acslX code to implement the Leggett and O’Flaherty models ([Lorenzana et al. 2005](#_ENREF_28)). Implementing the exposure model in Excel also removed the need to develop *de novo* computer code for the exposure model, and allowed development of exposure scenarios in Excel without the requirement for a license or knowledge of acslX. To assure that the interface between the Excel exposure model and the acslX biokinetics model is simple enough to not be disrupted by commercial evolution of either Excel or acslX, text files are used to pass data between the two platforms.

## 2.2 AALM Structure

The AALM predicts blood and tissue Pb masses (µg) and concentrations (µg/g) resulting from exposures to Pb in air, drinking water, surface dust, food, or miscellaneous Pb ingestion pathways. The AALM exposure module allows the user to simulate multi-pathway exposures that are constant or that vary in time increments as small as one day; and that occur at any age from birth to 90 years. The user can select to run a Pb biokinetics simulation based on either the Leggett (AALM-LG) or O’Flaherty (AALM-OF) biokinetics models. The ICRP Human Respiratory Tract Model (HRTM) deposition and absorption parameters are used in both the AALM-LG and AALM-OF. The user can select gastrointestinal absorption fractions for any age values as well as values for relative bioavailability (RBA) of Pb from all ingestion pathways.

The AALM software architecture consists of three components: (1) a macro-enabled Excel workbook (INPUT&OUTPUT.xlsm) that implements the exposure model and provides user access to all exposure and biokinetics parameters in the AALM; (2) an acslX program that implements a Leggett-based biokinetics model (AALM-LG.csl); and (3) an acslX program that implements an O’Flaherty-based biokinetics model (AALM-OF.csl). Required files, instructions for installing the files, and instructions on running the AALM are provided in a compressed zip file attached to this report (see Attachment A).

The data flow for AALM simulations is shown in Figure 1. The AALM simulation is implemented in acslX with AALM\_LG.csl (or AALM\_OF.csl). Input parameter values are selected by the user in a macro-enabled INPUT&OUTPUT Excel file (.xlsm). Macros in the INPUT&OUTPUT Excel file pass the input parameter values to a comma-delimited (CSV) text file (INPUT.DAT). Data in INPUT.DAT are imported into the AALM acslX program with acslX m-file scripts. Output variables from the simulation are passed from acslX to a CSV file (OUTPUT.DAT) and are read into the INPUT&OUTPUT Excel file with Excel macros.

AALM inputs and outputs are controlled and recorded in the *INPUT&OUTPUT.xlsm* workbook. This workbook has several functions: (1) allows setting of input parameter values for AALM simulations; (2) macros in this workbook are used to pass data to and from acslX; (3) allows plotting of AALM output data; and (4) provides a complete record of input values and results of each AALM simulation.

Worksheets in *INPUT&OUTPUT.xlsm* allow the user to set exposure scenarios for Pb in air (*Air*), surface dust, (*Dust*), drinking water (*Water*), food (*Food*) and/or other ingestion intakes (*Other*). Exposures can be discrete (i.e., a series of exposures at selected ages), and/or pulsed in a repeating frequency (e.g., 2 days/week for 3 months/year, for a selected age range). The AALM uses inputs from all exposure media when it creates biokinetics simulations. This allows construction of complex multi-pathway exposure scenarios having varying temporal patterns. Worksheets in *INPUT&OUTPUT.xlsm* also allow the user to set values for parameters that control Pb absorption and relative bioavailability in each medium (*RBA*), and biokinetics (*Lung*, *Systemic*, *Sex*). All settings are recorded in the *INPUT&OUTPUT.xlsm* workbook and can be recalled to re-run the simulation.

The two biokinetics models in the AALM have been modified from the originally reported Leggett ([1993](#_ENREF_27)) and O’Flaherty ([1993](#_ENREF_38), [1995](#_ENREF_39)) models. The important modifications include: (1) removal of all exposure components (moved to the Excel implementation); (2) implementation of a simplified version of the ICRP Human Respiratory Tract Model (HRTM; ICRP [1994](#_ENREF_20)) in both biokinetics models; (3) implementation of the O’Flaherty model growth algorithms in both biokinetics models to enable output of Pb concentrations in tissues in both models, and to unify blood and tissue volumes; and (4) implementation of relative bioavailability factors for ingested Pb from each exposure medium.

# 3.0 COMPARISON OF AALM-LG AND AALM-OF BIOKINETICS MODEL STRUCTURES

The AALM has two systemic biokinetics modules, one that is based on the Leggett ([1993](#_ENREF_27)) model (AALM-LG) and the other based on the O’Flaherty ([1993](#_ENREF_38), [1995](#_ENREF_39)) model (AALM-OF). Figures 2 and 3 show the structures of both models. Table 1 summarizes some of the major differences between the two modules. The most important difference is the way each model simulates Pb kinetics in bone. Both models represent kinetics of Pb in bone that are influenced by changes in the rates of bone turnover (bone formation and resorption). In general, the major features of bone Pb kinetics in both models are as follows: (1) relatively rapid transfers of Pb between plasma and bone forming surfaces; (2) increased bone Pb uptake during periods of bone growth; (3) incorporation of Pb into bone matrix and release of Pb from bone matrix during bone resorption; (4) maturation of bone associated with lower rates of bone turnover and related decreased mobility of Pb in bone matrix; and (5) more rapid turnover of trabecular bone Pb, relative to mature cortical bone. However, these processes are parameterized very differently in the two models.

AALM-LG simulates bone as a multi (6)-compartment system (see Figure 4) consisting of 3 cortical and 3 trabecular compartments that are distinguished by different Pb transfer rates: (1) relatively rapid exchange of Pb between diffusible plasma and surfaces of cortical and trabecular bone; (2) slower exchange of Pb at bone surfaces with an exchangeable Pb pool in bone volume; and (3) slow transfer of a portion of Pb in bone volume to a non-exchangeable pool that is released from bone to diffusible plasma only when bone is resorbed. Bone growth and maturation are simulated by age-dependent adjustments in rate coefficients for Pb transfers from plasma to bone surfaces, and from bone matrix to plasma. This approach simulates outcomes of the bone formation and resorption with bone Pb kinetics parameters, rather than simulating the underlying physiology of bone formation and resorption directly with parameters that govern formation and resorption.

AALM-OF simulates bone formation, resorption, and maturation of bone explicitly, and links these processes to uptake and release of Pb from bone (see Figure 5). In AALM-OF, bone turnover in cortical and trabecular bone is simulated with parameters that govern age-dependent bone formation and resorption of bone. Two phases of bone turnover are simulated. In juvenile bone, formation and resorption rates in cortical and trabecular bone are relatively high (high bone turnover) and formation dominates, resulting in bone growth, which ceases at age 25 years. In mature bone, formation and resorption rates are slower and bone formation rate equals resorption rate, resulting in remodelling, but no net growth of bone. Transfers of Pb into and out of trabecular bone are governed by age-dependent rates of bone formation and resorption, respectively. Cortical bone is assumed to consist of two regions: (1) metabolically active cortical bone in which Pb transfers are governed solely by rates of bone formation and resorption; and (2) mature cortical bone in which Pb undergoes exchange with bone calcium. The later process is simulated as bidirectional radial diffusion of Pb in between eight concentric shells of cortical bone.

The approach to modelling bone in AALM-OF (i.e., bone Pb kinetics as a function of bone physiological parameters) offers two major advantages: (1) inclusion of parameters that control bone physiology (e.g., growth, volume, maturation) supports simulation of changes to bone mineral metabolism that might affect bone production, growth, or maturation (e.g., disease, nutrition, menopause, weightlessness), and predictions of the effects that these changes might have on bone Pb kinetics. An analogous simulation in the AALM-LG requires direct knowledge (or assumptions) of the effects of these changes on bone Pb transfer coefficients; and (2) advances in the knowledge of bone physiology (e.g., metabolism, growth, resorption, disease) and of bone kinetics for other elements (e.g., calcium, strontium) can be incorporated into the model to improve the parameterization and parameter values of the model, and its capability to simulate and predict bone growth, volume, and maturation. In contrast, specialized studies for all the different age related scenarios would be needed to improve values for the less physiologically representation of bone Pb kinetics in the AALM-LG model based on compartment transfer rates that change with age.

# 4.0 COMPARISON OF AALM-LG AND AALM-OF BLOOD AND TISSUE PB PREDICTIONS

Differences in the structures of the Leggett and O’Flaherty biokinetics models would be expected to result in different predictions of blood and tissue Pb levels for similar Pb exposure assumptions ([Maddaloni et al. 2005](#_ENREF_29)). The revised AALM provides a convenient platform for comparing the models, because it allows both to be run using the same exposure and absorption settings. Two types of comparisons were made of AALM-LG and AALM-OF: (1) age profiles for blood and tissue Pb levels following an exposure to a constant Pb intake (µg/day) were simulated and compared; and (2) dose-response relationships between ingested dose and Pb levels were compared by simulating a series of increasing Pb intakes. In either type of simulation, parameters that control Pb absorption and growth were set to the same values (defaults for AALM-OF), so that differences in blood and tissue Pb levels could be attributed entirely to differences in the simulation of systemic (post-absorption) biokinetics.

## 4.1 Comparison of Model Predictions for Constant Pb Intake

Figures 6 thru 9 show results of the simulations for a constant ingestion of 5 µg Pb/day beginning at birth and extending to age 30 years. This exposure results in predicted blood Pb concentrations less than 5 µg/dL, which is well below the concentration at which saturation of uptake into red blood cells significantly affects blood Pb levels (see Section 4.2). Figure 6 shows the age profiles for selected output variables (µg Pb in blood, bone, soft tissue and total body). Figure 7 shows the differences expressed relative to the AALM-LG (arbitrarily selected as the reference for presentation of the results). A negative value in Figure 7 indicates that the prediction from AALM-OF is less than that from AALM-LG. For example, ‑0.65 in Figure 7 indicates that the AALM-OF blood Pb prediction is less than the AALM-LG prediction, and the magnitude of the difference is 65% relative to the AALM-LG value. Figure 8 compares elimination rates following cessation of exposure. Figure 9 compares predicted cumulative urinary and fecal Pb excretion.

Several differences between the models are evident from these comparisons.

* AALM-OF predicts lower blood Pb levels prior to age 10 years (64–65%), after which, the models begin to converge on similar blood Pb levels, with adult predictions from the AALM-OF exceeding AALM-LG by approximately 20%.
* AALM-OF predicts lower bone Pb levels in children prior to age 10 years (63–68%), after which, the models begin to converge on similar bone Pb levels, with adult predictions from the AALM-OF exceeding AALM-LG by approximately 18%.
* AALM-OF predicts lower soft tissue Pb levels (all tissues combined, excluding bone) at all ages (59–92%).
* Both models predict similar accumulation of Pb over the lifetime, reflected in similar total body burdens (agreement is within 10%).
* With cessation of exposure, both models predict rapid declines of Pb in blood (t1/2=30–50 days) and soft tissue, with a slower decline in bone Pb (t1/2 10–20 years).
* Both models predict multiple rates of decline in blood Pb. In adults, the half-time for the first 50 days following cessation of exposure is approximately 36 days in AALM-LG and 46 days in AALM-OF. The half-time for the period 5–20 years following cessation of exposure is 12.7 years in AALM-LG, and 10.9 years in AALM-OF. The slow phase results from transfer of bone Pb to blood.
* Both models predict a more rapid decline in bone Pb in children compared to adults following cessation of exposure. The two models predicted similar half-times for bone Pb elimination in children (t1/2 = 3.00 [AALM-LG], 2.24 years [AALM-OF]).
* Although both models predict slower elimination of Pb from bone in adults, AALM-OF predicts a more rapid decline (t1/2 = 12.6 year) than AALM-LG (t1/2 = 19.7 year).
* AALM-OF predicts a higher rate of urinary excretion of Pb compared to AALM-LG. Fecal excretion is identical in both models because it is dominated by unabsorbed Pb and gastrointestinal absorption parameters were set to the same values in both models for the comparison simulations.

Amounts of Pb in tissues are converted to Pb concentrations in both models by dividing Pb masses by age-dependent values for tissue weights. The latter are predicted in both models from the body growth and tissue growth models developed by O’Flaherty ([1995](#_ENREF_39)). The blood and bone Pb concentrations predicted for an exposure to 5 µg Pb/day are shown in Figure 10. Differences in the model predictions of tissue Pb masses are reflected in the tissue Pb concentrations. The magnitudes of the differences between models (i.e., ratio AALM-LG/AALM-OF) are the same for Pb masses and concentrations, because both models use the same tissue growth algorithms, which predict the same tissue volumes and weights.

## 4.2 Comparison of Predicted Dose-Response for Blood and Tissue Pb

Although both AALM-LG and AALM-OF are mathematically linear models (i.e., all state variables are defined with linear differential equations), they predict curvilinear dose-response relationships for blood Pb resulting from a saturable capacity of red blood cells (RBC) to take up Pb. Dose-response relationships predicted from AALM-LG and AALM-OF are shown in Figures 11 and 12, for children (age 5 years) and adults (age 30 years), respectively. Although curvature of the dose-response relationship for blood derives from saturation of uptake of Pb in RBCs, the two models use different computational approaches to model the saturable uptake. AALM-LG simulates binding of Pb in red blood cells with rate coefficients for transfer of Pb from plasma to RBCs (child and adult, t1/2=0.0014 days), and from RBCs to plasma (child t1/2=2.5 days, adult t1/2=5 days). This results in a rapid uptake, slower release, and accumulation of RBC Pb. The plasma-blood concentration ratio is governed, in part, by the ratio of these transfer coefficients (plasma to RBC/RBC to plasma). The higher ratio in children (i.e., exit rate is faster) results in higher plasma-RBC concentration ratios in children. Above a non-linear, threshold Pb concentration in red blood cells (60 µg/L), the rate constant for transfer into RBCs declines with increasing intracellular concentration, approaching zero (no uptake) at a saturating concentration of 350 µg/dL RBC (see Equation 1).

1.5 Eq. (1)

where *TOORBC* is the deposition fraction from diffusible plasma to red blood cells; TORBC the age scaled deposition fraction from diffusible plasma to red blood cells below non-linear threshold; *RBCCONC* the red blood cell Pb concentration (µg/dL RBC volume); *RBCNL* the non-linear uptake kinetics threshold concentration (µg Pb/dL RBC volume); and *SATRAT* the maximum capacity of the red blood cell compartment (µg Pb/dL RBC volume).

AALM-OF simulates a binding equilibrium (rather than kinetics) in which Pb in plasma achieves instantaneous equilibrium with unbound Pb in red blood cells, which is in equilibrium with bound Pb. Binding parameters include a maximum capacity (270 µg Pb/dL RBC) and half saturation concentration (0.75 µg/dL RBC), with the relationship represented as follows (see Equation 2):

Eq. (2)

where *CB* is the blood Pb concentration (µg/dL), *CP* the plasma Pb concentration (µg/dL); *HCT* is the haematocrit; *G* the ratio of unbound red blood cell Pb to plasma Pb; *BIND* the maximum capacity of red blood cell binding (µg/dL); and *KBIND* the half saturation coefficient (µg/dL). One advantage of this approach is that the parameters BIND and KBIND have a direct empirical basis, as they have been estimated from data on Pb concentrations in plasma and red blood cells (e.g., [Bergdahl et al. 1998](#_ENREF_5); [O’Flaherty 1993](#_ENREF_38)). However, a disadvantage is that it represents plasma-RBC kinetics as essentially being instantaneous; whereas, observations made following injection of radiolead suggest that kinetics may be slower and more complex (see [Leggett 1993](#_ENREF_27) for discussion of these observations).

The different parameterizations of red blood cell saturation are evident in the relationships between plasma and blood Pb predicted from the two models. In both models, the plasma-blood concentration ratio increases with increasing blood Pb concentration, as the red blood cell approaches saturation. In AALM-OF, the plasma-blood Pb ratio below saturation remains nearly constant with age (0.007); whereas, in AALM-LG, the plasma:blood ratios are higher in children compared to adults. AALM-LG predicts a plasma-blood ratio that declines from 0.01 at age 1 year to 0.003 at ages beyond 10 years (below saturation).

Both models predict linear dose-response relationships for bone Pb, and for all other tissue Pb The predicted dose-response relationships for bone are more similar in adults, whereas, AALM-LG predicts a steeper dose-response relationship for bone in children. The steeper dose-response relationship for bone Pb in children occurs in AALM-LG even though the elimination rates from bone are similar in both models. This suggests that the differences between model results for bone Pb is related to the rates of deposition of Pb in bone, rather than to differences in rates of bone Pb elimination.

# 5.0 SENSITIVITY ANALYSIS OF AALM-LG AND AALM-OF

Relative to the AALM-LG, AALM-OF predicts lower amounts and concentrations of Pb in blood in children, higher amounts and concentrations of Pb in blood in adults, and lower amounts and concentrations of Pb in soft tissues in at all ages. Numerous individual parameters or combinations of parameters could contribute to these differences. AALM-LG has 39 parameters and AALM-OF has 35 parameters that collectively determine the biokinetics of absorbed Pb in each model to varying degrees. These parameters and their nominal values are presented in Tables 2 and 3. A univariate sensitivity analysis was conducted to determine the effect of each parameter on predictions of Pb in blood, bone, and soft tissues.[[1]](#footnote-1) The sensitivity analysis consisted of running each model before and after perturbing values for single parameters by a factor of 0.01, in the up and down directions. Parameter sensitivities were assessed by comparing standardized sensitivity coefficients (see Equation 3):

 Eq. (3)

where *SSC* is the standardized sensitivity coefficient; *f(x)* the output variable (e.g., blood Pb) at parameter value *x*; and *∆* the perturbation of *x* (e.g., 0.01x). Values for SSC were determined for blood, bone, and soft tissue Pb at ages selected to represent children (5 years) or adults (30 years).

## 5.1 Sensitivity Analysis of AALM-LG

SSCs were derived for all input parameters to AALM-LG other than those that control Pb absorption or growth. Separate sensitivity analyses were run to determine parameter sensitivity of the total amount of Pb in blood, bone, liver, kidney, or other soft tissues, in children (age 5 years) and adults (age 30 years). SSCs are displayed in order of highest to smallest value for adults in Tables 4 thru 8. Larger values of SSC indicate larger effects of the parameter on blood Pb. For example, blood Pb is most sensitive to the value of the parameter *TEVF*, the deposition fraction for Pb transfer from diffusible plasma to the extravascular fluid (see Table 4). The value 8.38 indicates that a 1% change in *TEVF* results in an 8.38% change in blood Pb. Influential parameters have SSCs that exceed 0.1 (>0.1% change in tissue Pb per 1% change in the input parameter).

In the discussion that follows, input parameter values are expressed as their equivalent first-order transfer rates (day-1) and their corresponding approximate first-order half-times (t1/2, day). These values are shown in Table 2. In AALM-LG, the central distribution compartment is diffusible plasma, which exchanges Pb with other tissue compartments. Input parameters that control transfers of Pb from tissues to diffusible plasma are expressed as first-order rates. Input parameters that control transfers from diffusible plasma to tissues are expressed as deposition fractions. Deposition fractions represent the fractional apportionment of the total outflow of Pb from diffusible plasma ([Leggett 1993](#_ENREF_27)). First-order rates are derived in the AALM-LG as the product of deposition fraction and total outflow of Pb from the diffusible plasma compartment (*RPLAS*, see Equation 4).

Eq. (4)

where *REFV* is the transfer rate from diffusible plasma to the extravascular fluid (day-1); *TEFV* the deposition fraction for transfer to the extravascular fluid; and *RPLAS* the total rate of transfer of Pb to all tissues (day-1). The nominal value for *RPLAS* is 2000 day-1. If the deposition fraction for *TEFV* is 0.5, the corresponding transfer rate for *TEFV* is 1000 day-1 (0.5 x 2000 day-1). Values for transfer rates corresponding to deposition fractions are presented in Table 2, so that they can be directly compared to the return transfer rates from tissue to diffusible plasma. The values for the corresponding depositions fractions can be calculated from Equation 4.

### 5.1.1 Influential Parameters Common to All Tissues

Several parameters had relatively large influences (SSC >0.1) across all or most of the tissues that were included in the sensitivity analysis and dominate Pb biokinetics in the AALM-LG. These parameters are *TEVF*, *TORBC*, *TOSOF0*, *TOLVR1*, *H1TOBL*, and *TBONE*.

The parameter *TEVF* controls the rate of transfer of Pb from diffusible (non-bound) plasma to the extravascular space. The nominal value for the rate is 1000 day-1 (t1/2=1.0 min) or approximately one half of the total transfer rate out of diffusible plasma to all tissues (2000 day-1). The return rate to diffusible plasma is 333 day-1 (t1/2=3.0 min). This results in a rapid exchange of Pb in diffusible plasma with the extravascular fluid, with an equilibrium ratio in which the extravascular fluid contains approximately 3 times the amount of Pb in diffusible plasma. The extravascular fluid serves as a rapid exchange reservoir that contributes to plasma Pb. Increasing or decreasing the value of *TEVF* increases or decreases, respectively, the amount of Pb in plasma and, thereby, blood Pb and the amount of Pb available for distribution to other tissues. The prominence of *TEVF* in the SSCs for all tissues may also result from its use in age scaling of deposition fractions in the model. Deposition fractions for all tissues other than bone are scaled as function of *TEVF* and *TBONE* (the deposition fraction to bone surfaces) (see Equation 5).

Eq. (5)

where *TBONEL* is the terminal value for *TBONE* on the last day of the simulation. The *AGESCL* variable adjusts the deposition fractions (and total outflow) from diffusible plasma to soft tissues so that their sum does not exceed total outflow (*TEFV*), while outflow to bone (*TBONE*) varies with age. As a result of its use to age scale deposition fractions, changes to *TEVF* affects Pb kinetics of red blood cell, kidney, liver, and other soft tissues.

The parameters *TORBC* and *RRBC* control the transfer rates of Pb into and out of red blood cells, respectively. The nominal values in adults are 480 day-1 (t1/2=2.1 min) and 0.139 day-1 (t1/2=5.0 day). The equilibrium ratio (*TORBC/RRBC*) is approximately 3450, which results in accumulation of Pb in the RBC, relative to plasma, and Pb in red blood cells being the dominant contributor to blood Pb. Increasing the transfer rate into red blood cells (*TORBC*), without a change in the return rate (*RRBC*) increases blood Pb, whereas, increasing the transfer rate out of red blood cells (*RRBC*), makes more Pb available to the diffusible plasma compartment for distribution to other tissues, and decreases blood Pb.

AALM-LG has three soft tissue compartments, representing fast (*SOF0*), moderate (*SOF1*), and slow (*SOF2*) kinetic pools of Pb in soft tissues other than blood, kidney, or liver. The parameter *TOSOF0* controls the rate of transfer from diffusible plasma to the fast compartment. The nominal value in adults is 178 day-1 (t1/2=5.6 min) and the return rate is 2.08 day-1 (t1/2=8.0 hours). Similar to the extravascular fluid, this soft tissue compartment provides an exchange reservoir to support plasma and blood Pb, as well as Pb available for distribution to other tissues.

The parameters *TOLVR1* and *H1TOBL* control the transfer of Pb from diffusible plasma to liver and the return to plasma, respectively. Nominal values are 80 day-1 (t1/2=12.5 min) for transfer to liver and 0.03 day-1 (t1/2=23.1 day) for return. Similar to the rapid exchange soft tissue compartment, this liver compartment provides a reservoir to support plasma and blood Pb.

The parameter *TBONE* controls the transfer rate from diffusible plasma to surface bone, the only pathway for entrance of Pb into bone where it can be sequestered into slower kinetic pools of bone volume. The nominal values are 89 day-1 and 71 day-1 (t1/2=11.2 min, 14.1 min) for trabecular and cortical bone, respectively. The return value from both types of bone is 0.5 day-1 (14 day). More than 90% of the Pb body burden resides in bone, as a result, the transfer to bone affects Pb levels in all other tissues. The terminal value of *TBONE* (*TBONEL*) is also used in the age scaling of deposition fractions to all tissues other than bone (see Equation 5). This is reason why it shows up as an influential parameter across all tissues.

### 5.1.2 Sensitivity Analysis of AALM-LG Blood Pb Predictions

AALM-LG SSCs for blood Pb (*ABLOOD*) are shown in Table 4. The most influential parameters on blood Pb (SSCs >0.1) are *TEFV*, *TORBC*, *TOSOF0*, *RRBC*, *TOLVR1*, *H1TOBL*, and *TBONE*. These parameters have SSCs >0.1 across all tissues (see Section 5.1.1).

### 5.1.3 Sensitivity Analysis of AALM-LG Bone Pb Predictions

AALM-LG SSCs for bone Pb (*ABONE*) are shown in Table 5. The most influential parameters on bone Pb (SSCs >0.1) are *TEFV*, *TORBC*, *TBONE*, *TOSOF0*, *FLONG*, *RCS2DF*, *TOLVR1*, *H1TOBL*, and *RTS2DF*. The bone model in AALM-LG includes three sub-compartments for cortical and trabecular bone that represent fast (surface bone), moderate (exchangeable), and slow (non-exchangeable) Pb pools (see Figure 3). The slow compartment contains most (>90%) of the Pb in bone and, therefore, is the major determinant of the amount of Pb in bone. The parameter *FLONG* controls the rate of transfer of Pb from the moderate to the slow compartment. Lead enters the moderate and slow bone compartments from surface bone, which is in direct exchange with plasma. The parameter *TBONE* controls the rate of transfer of Pb to bone surfaces; nominal values are 89 day-1 and 71 day-1 (t1/2=11.2 min, 14.1 min) for trabecular and cortical bone, respectively. The parameters *RCS2DF* and *RTS2DF* control the rate of return of Pb from bone surface to plasma (0.5 day-1, t1/2=1.4 day).

### 5.1.4 Sensitivity Analysis of AALM-LG Liver Pb Predictions

The most influential parameters on liver Pb (SSCs >0.1) are *TEFV*, *TORBC*, *TOSOF0*, *TOLVR1*, *H1TOH2*, *RLVR2*, *H1TOBL*, and *RLVR1* (see Table 6). The liver model in AALM-LG includes two sub-compartments representing fast (H1) and slow (H2) pools. Lead in the fast compartment exchanges with plasma and delivers Pb into the slow compartment and to bile. Transfer of Pb into the fast compartments controlled by the parameter *TOLVR1* (80 day-1, t1/2=11.2 min) and return to plasma is controlled by *RLVR1* (0.0312 day-1, t1/2=22.2 day). Transfer of Pb from the fast to the slow compartment is controlled by *H1TOH2* (0.00693 day-1, t1/2=100 day) and transfer to bile is controlled by *H1TOBL* (0.0312day-1, 22.2 day). Return of Pb to plasma is controlled by *RLVR2* (0.0019 day-1, t1/2=365 day).

### 5.1.5 Sensitivity Analysis of AALM-LG Kidney Pb Predictions

The most influential parameters on kidney Pb (SSCs >0.1) are *TEFV*, *TORBC*, *TOSOF0*, *RKDN2*, *TOKDN1*, *TOKDN2*, *RKDN2*, *TOLV1*, and *H1TOBL* (see Table 7). The kidney model in AALM-LG includes two sub-compartments representing urinary route through the kidney (RK1) and a storage compartment that exchanges with plasma (RK2) pools. Transfer of Pb into kidney is controlled by the parameters *TOKDN1* (40 day-1, t1/2=25 min) and *TOKDN2* (0.4 day-1, t1/2=1.7 day). Return of Pb to plasma is controlled by the parameter *RKDN2* (0.0019 day-1, t1/2=365 day).

### 5.1.6 Sensitivity Analysis of AALM-LG Other Soft Tissue Pb Predictions

The most influential parameters on other soft tissue Pb (SSCs >0.1) are *TEFV*, *TORBC*, *TOSOF0*, *RSOF2*, *TOSOF2*, *TOLVR1*, *H1TOBL*, *TOSOF1*, and *RSOF1* (see Table 8). AALM-LG has three soft tissue compartments, representing fast (SOF0), moderate (SOF1), and slow (SOF2) kinetic pools of Pb in soft tissues other than blood, kidney, or liver. Transfer into each compartment is controlled by parameters TOSOF0 (178 day-1, t1/2=5.6 min), *TOSOF1* (10 day-1, 1.7 hours), and *TOSOF2* (2 day-1, t1/2=8.3 hours). Return of Pb to plasma is controlled by parameters *RSOF0* (2.08 day-1, t1/2=8.0 hours), *RSOF1* (0.00416 day-1, t1/2=167 day), and *RSOF2* (0.00038 day-1, 1824 day).

## 5.2 Sensitivity Analysis of AALM-OF

SSCs were derived for all input parameters to AALM-OF other than those that control Pb absorption or growth. Separate sensitivity analyses were run to determine parameter sensitivity of the total amount of Pb in blood, bone, liver, kidney, or poorly-perfused and well-perfused tissues, in children (age 5 years) and adults (age 30 years). Input parameter values for AALM-OF are presented in Table 3. This is a mix of parameters for Pb, and parameters that control bone formation and resorption rates that determine transfer of Pb in and out of deep bone. SSCs for each tissue are displayed in order from highest to smallest value for adults in Tables 9 thru 14.

### 5.2.1 Influential Parameters Common to All Tissues

Three parameters had large influences (SSC >0.1) across all, or most, of the tissues that were included in the sensitivity analysis, and dominate Pb kinetics in the AALM-OF. These parameters are C1, C2, and C3. Urinary excretory clearance of Pb from plasma is simulated in AALM-OF as a function of glomerular filtration rate (GFR). The parameters *C1*, *C2*, and *C3* are unitless parameters in the function that simulates GFR as a function of age. Changes to these parameters alter the rate of removal of Pb from plasma to urine and, thereby, the amount of Pb in blood and available for distribution to other tissues.

### 5.2.2 Sensitivity Analysis of AALM-OF Blood Pb Predictions

The most influential parameters on blood Pb (SSCs >0.1) are *C1*, *C2*, *BIND*, *KBIND*, and *C3* (see Table 9). Uptake of Pb into red blood cells is simulated in AALM-OF as a binding equilibrium between plasma Pb and red blood cell Pb (see Section 2.2). The parameters *BIND* (2.7 mg/L) and *KBIND* (0.0075 mg/L) are the maximum binding capacity of the red blood cells, and the half saturation concentration of Pb for binding, respectively. Changing *BIND* or *KBIND* affects the amount of Pb sequestered in red blood cells, and the amount of Pb available to the plasma compartment for distribution to other tissues. Increasing *BIND* increases red blood cell binding, and increases blood Pb. Increasing *KBIND* increases the plasma Pb concentration needed to achieve a given RBC Pb concentration, and decreases blood Pb.

### 5.2.3 Sensitivity Analysis of AALM-OF Bone Pb Predictions

The most influential parameters on bone Pb (SSCs >0.1) are *C1*, *C2*, *R0*, *RAD8*, *EXPO*, and *C3* (see Table 10). The parameter *R0* controls the clearance of Pb from bone into the vascular sites in bone (canalicule) where exchange with plasma occurs. The nominal value is 5E-7 cm3/day. Increasing *R0* decreases bone Pb. The parameter *RAD8* is the radius of the deepest (eight of 8) diffusion shells in mature cortical bone. This parameter determines the diffusion volume (2.14E-3 cm) and, thereby, the clearance of Pb from the deepest bone compartment. Increasing *RAD8* decreases bone Pb. The parameter *EXPO* is a unitless exponent constant in the function that simulates the age-dependency of the bone volume participating in adult remodelling. During adult remodelling, bone formation and resorption rates are slower than during child and adolescent growth periods. As a result, exchange of Pb between deep bone deposits and plasma is slower in mature bone than during growth.

### 5.2.4 Sensitivity Analysis of AALM-OF Liver Pb Predictions

The most influential parameters on liver Pb (SSCs >0.1) are *C1*, *C2*, *PL*, and *C3* (see Table 11). Exchange of Pb between plasma and liver is simulated in AALM-OF as a flow-limited process determined by the liver/plasma partition coefficient and blood flow to the liver. The parameter *PL* is the liver/plasma partition coefficient (*PL*=50). The nominal value is 50. Increasing *PL* increases liver Pb.

### 5.2.5 Sensitivity Analysis of AALM-OF Kidney Pb Predictions

The most influential parameters on kidney Pb (SSCs >0.1) are *C1*, *C2*, *PK*, and *C3* (see Table 12). Similar to liver, exchange of Pb between plasma and kidney is simulated in AALM-OF as a flow-limited process determined by the kidney/plasma partition coefficient (*PK*=50) and blood flow to the kidney. Increasing *PK* increases kidney Pb.

### 5.2.6 Sensitivity Analysis of AALM-OF Poorly-Perfused Tissue Pb Predictions

The most influential parameters on poorly-perfused tissue Pb (SSCs >0.1) are *C1*, *C2*, *PP*, and *C3* (see Table 13). Exchange of Pb between plasma and poorly-perfused tissue is simulated in AALM-OF as a flow-limited process determined by the tissue/plasma partition coefficient (*PP*=2.0) and blood flow to the tissue. Increasing *PP* increases poorly-perfused tissue Pb.

### 5.2.7 Sensitivity Analysis of AALM-OF Well-Perfused Tissue Pb Predictions

The most influential parameters on well-perfused tissue Pb (SSCs >0.1) are *C1*, *C2*, *PW*, and *C3* (see Table 14). Exchange of Pb between plasma and well-perfused tissue is simulated in AALM-OF as a flow-limited process determined by the tissue/plasma partition coefficient (*PW*=50) and blood flow to the tissue. Increasing *PW* increases well-perfused tissue Pb.

# 6.0 CONCLUSIONS FROM MODEL COMPARISONS AND SENSITIVITY ANALYSES

Table 15 lists the major differences between predictions from AALM-LG and AALM-OF and corresponding parameter values that had the highest SSCs for each prediction. Data may exist for some of the significant parameters that would allow evaluation and/or optimization of parameter values. AALM-OF parameters *C1* and *C2* control glomerular filtration rate, and thereby, urinary clearance of Pb from plasma. Abundant data exist on rates and age (i.e., body size) dependence of glomerular filtration in humans (e.g., [Peters 2004](#_ENREF_44); [Peters et al. 2000](#_ENREF_43)). Data on urinary clearance of Pb in humans also exist that may be useful for evaluating model predictions (e.g., [SRC 1997](#_ENREF_53)).

AALM-OF parameters *BIND* and *KBIND* and AALM-LG parameters *TORBC* and *RRBC* control uptake of Pb into red blood cells and, thereby, influence plasma Pb and its distribution to tissues. These parameters can be evaluated against data from studies in which levels of Pb in plasma and whole blood (and/or red blood cells) have been measured in humans with methods that ensure sampling of plasma Pb without contamination with Pb from lysed red cells (e.g., [SRC 2003](#_ENREF_54)).

Direct empirical evaluation of AALM-OF and AALM-LG parameters that control bone Pb may not be feasible because of lack of data to directly estimate parameter values. However, optimization of influential parameters that control bone Pb levels and relationships between blood and bone Pb may be feasible with data from long-term monitoring studies of blood and bone, where exposure to Pb was abruptly changed (e.g., retried Pb workers; see U.S. EPA [2013](#_ENREF_58)).

Similarly, direct empirical evaluation of AALM-OF tissue-plasma partition coefficients, and AALM-LG transfer rates and deposition fractions that control Pb levels in liver, kidney, and other soft tissues may not be feasible because of lack of data to directly estimate parameter values. However, it may be possible to optimize these parameters against data from cadaver studies in which the distribution of Pb body burden in bone and soft tissue has been measured.

# 7.0 EVALUATION AND OPTIMIZATION OF THE AALM

Although the sensitivity analyses described in Section 5.0 provide some insight regarding the parameters that contribute to differences in predictions from the two models; a more important objective is to determine what set of parameters provides the most accurate representation of observations of Pb kinetics in humans. Extensive documentation of the development and calibration of the Leggett and O’Flaherty models has been reported ([Leggett 1993](#_ENREF_27); [O’Flaherty 1993](#_ENREF_38), [1995](#_ENREF_39), [1998](#_ENREF_40), [2000](#_ENREF_42); [O’Flaherty et al. 1998](#_ENREF_41)). New data have become available since the development of the models (U.S. EPA [2013](#_ENREF_58)). Important objectives for further development of the AALM are: (1) collect and re-examine all available data for utility in model evaluation, optimization, and validation; (2) conduct a comprehensive evaluation of the models against a common set of data; (3) optimize influential parameters identified in Section 5 that can be informed by the observation data sets; and (4) validate the model against a set of observations not utilized in optimization of the models.

Searches for studies of the toxicokinetics of Pb in humans that provide data that might be useful for estimated model parameter values were conducted. Three types of data were of particular interest: (1) blood, tissue, or excreted Pb paired with measured Pb intakes and/or exposures; (2) temporal patterns of blood, tissue, or excreted Pb following an abrupt change in Pb intake or exposure; and (3) paired data for blood and tissues or excreted Pb (e.g., urine/blood or tissue/blood ratios). The studies and pertinent digitized data have been collected in a bibliographic library (Endnote®) attached to this report (see Attachment B). Based on the available data retrieved and processed from the searches as well as considerations of the results of comparisons of the two models, a stepwise optimization approach was developed, in which specific outputs of the models were evaluated against observations in humans, and key parameters were optimized to achieve agreement with the observations (see Table 16). Optimized values for all input parameters that control post-absorption kinetics in the AALM are provided in Attachment A.

Optimization was achieved using maximum likelihood (MLE) algorithms available in acslX (e.g., Nelder Mead) or if this was not possible, by visual inspection. Optimizations were evaluated by inspection of residuals (Equation 6) and the r2 for the least squares linear regression of observed and predicted values.

Eq. (6)

The optimization objectives were residuals ≤ ±2 and r2>0.70.

## 7.1 Unification of Simulation of GI Absorption and Growth

A goal of the optimization was to determine if AALM-LG and AALM-OF would converge on similar predictions for post-absorption kinetics of blood and tissue Pb concentrations. To remove effects of differences in absorption and growth parameters in the two biokinetics modules, the GI absorption and growth parameters from the O’Flaherty ([1993](#_ENREF_38), [1995](#_ENREF_39)) model were adopted for both AALM sub-models. The resulting AALM GI absorption model is a continuous function (Equation 7) that simulates an age-dependent decline in the absorption fraction (*AFAge*), from the value in infancy to the value in adults.

Eq. (7)

The default settings (AFC1=0.60, AFC2=0.52) result in AF=0.58 at birth and AF=0.08 in adults (see Figure 13).

Tissue growth in the AALM is simulated as a function of body weight, which is age-dependent (see Figure 14). Tissue Pb concentrations are calculated as the Pb mass (µg) divided by the tissue weight (g). Concentrations of Pb in bone wet weight are converted to concentration per g bone mineral by dividing the wet weight concentration by the ash fraction of bone. This conversion was used to compare model predictions with bone X-ray fluorescence (XRF) data, which is typically reported in units of Pb per g bone mineral. Bone ash fractions were assumed to be 0.55 and 0.50 for cortical and trabecular bone, respectively (ICRP [1981](#_ENREF_18)).

## 7.2 Optimization of Plasma Pb – Blood Pb Relationship

Six studies provided data on individual human subjects that can be used to evaluate the relationship between plasma Pb and blood Pb concentrations. Measurements of plasma Pb were made using either inductively coupled plasma mass spectrometry ([Bergdahl et al. 1997](#_ENREF_4), [1998](#_ENREF_5), [1999](#_ENREF_6); [Hernández-Avila et al. 1998](#_ENREF_15); [Schütz et al. 1996](#_ENREF_49); [Smith et al. 2002](#_ENREF_51)) or stable isotope dilution with thermal ionization mass spectrometry ([Manton et al. 2001](#_ENREF_33)). In all of these studies, methods were employed to control for sample contamination, which is of particular importance in measurements of the low Pb levels found in plasma. Taken together, the observations from these reports varied over a wide range of blood Pb (approximately 0.34–94.8 μg/dL) and plasma Pb (approximately 0.0014–1.92 μg/dL) levels. These studies provided 406 individual measurements of plasma Pb and blood Pb, in adult workers as well as individuals with no known history of occupational exposure to Pb ([SRC 2003](#_ENREF_54)). Only one study provides similar data in children ([Bergdahl et al. 1999](#_ENREF_6)). The observations in children do not appear to differ substantially from those for adults.

A best fit (least-squares) model for combined data from the above six studies was identified, and is presented in Equation 8:

(r2=0.90) Eq. (8)

AALM-OF parameters KBIND and BIND were optimized (Nelder Mead) against this data set in the AALM-OF function relating plasma Pb and blood Pb (Equation 9):

Eq. (9)

AALM-LG parameter RBCNL was optimized by visual inspection (it was not possible to derive an independent expression for the plasma Pb and blood Pb relationship because relevant parameters control rate constants for transfer of Pb between plasma and RBC compartments).

Figures 15 compares the observed and predicted whole blood and plasma Pb in adults relationship. Residuals for the optimized models are within acceptable limits (-2, 2). The r2 values for predictions are 0.99 and 0.98.

## 7.3 Optimization of Plasma-to-Urine Pb Clearance

Four studies provide data to derive estimates of the Pb plasma-to-urine clearance rate (L/day) ([Araki et al. 1986](#_ENREF_1); [Chamberlain et al. 1978](#_ENREF_10); [Manton and Malloy 1983](#_ENREF_31); [Manton and Cook 1984](#_ENREF_32)). Clearance estimates from these studies are reported in SRC ([1992](#_ENREF_52)). These estimated clearance rates are based on measurements made in a total of 32 (“normal”subjects). The mean of the estimates from the four studies is 18 L/day ± 4 (SD).

Rentschler et al. ([2011](#_ENREF_47)) reported individual subject data on urinary excretion of Pb (µg/g creatinine) and plasma Pb concentration in in five cases of Pb poisoning (blood Pb>80 µg/dL). The cases were followed for periods up to 800 days. If assumptions are made about body weight (not reported) and established associations between creatinine excretion and lead body mass, clearance rates can be estimated from these data. The estimated mean plasma clearance was 43 L/day ±13 (SD) (range: 32–64 L/day). Lead poisoning may have been a contributing factor to the relatively high clearances based on Rentschler et al. ([2011](#_ENREF_47)). Therefore, for the purpose of model optimization, 18 L/day was selected as the representative value for plasma-to-urine clearance.

In AALM-OF, urinary excretion of Pb is an age-dependent fraction of GFR. Parameters for the GFR function were modified to achieve an adult GFR of approximately 170 L/day/1.73m2 (120 mL/min/1.73 m2 body surface area, ICRP [1981](#_ENREF_18)), with infant (<1 year) values 30% of the adult value ([DeWoskin and Thompson 2008](#_ENREF_11)). AALM-OF parameters C2 and C3 were optimized in a function relating age and total Pb excretory clearance (FRX) as shown in Equation 10.

) Eq. (10)

AALM-LG parameters TKDN1 and TOURIN were optimized by visual inspection.

Figure 16 compares predicted and observed urinary clearance in adults. No data are available to evaluate the different age patterns for urinary clearance predicted by AALM-LG and AALM-OF.

## 7.4 Optimization of Soft Tissue-to-Bone Pb Ratio

Four studies provide data for measurements of post-mortem soft tissue and bone Pb concentrations ([Barry 1975](#_ENREF_2),[1981](#_ENREF_3), [1981](#_ENREF_3); [Gerhardsson et al. 1995](#_ENREF_13); [Gross et al. 1975](#_ENREF_14)). Gerhardsson et al. ([1995](#_ENREF_13)) reported only soft tissue Pb concentrations; whereas, the other three studies reported soft tissue and bone Pb concentrations that can be used to estimate the ratios. Barry ([1975](#_ENREF_2), [1981](#_ENREF_3)) reported data for children and adults in age brackets, so the data from Barry ([1975](#_ENREF_2)) was used as the primary source to optimize parameters for kidney/bone and liver/bone Pb ratios as a function of age.

Barry ([1975](#_ENREF_2)) reported data on tibia Pb concentrations that are simulated as cortical bone concentrations in the AALM models. Since Barry ([1975](#_ENREF_2)) reported group mean tissue concentrations (not ratios in autopsy cases), the mean tissue to bone ratios were approximated from the group means.

In AALM-OF, uptake of Pb into kidney, liver, and other well-perfused tissue is assumed to be flow-limited and governed by blood flow and the tissue/plasma partition coefficients, PK, PL, and PW. Attempts to optimize these three parameters failed to accurately simulate the decline in the tissue/bone ratios predicted from the Barry ([1975](#_ENREF_2)) observations. An improved fit was achieved when the constants PK, PL, and PW were allowed to vary with age according to the function shown in Equation 11.

Eq. (11)

The parameters PKC and PKA (for kidney), PLC and PLA (for liver), and PWC and PWA (for other well-perfused) were optimized (Nelder Mead) against the tissue/cortical bone ratios derived from the data reported in Barry ([1975](#_ENREF_2)).

AALM-LG parameters TOKDN2 and RKDN2 (for kidney) and RLVR2 (for liver) were optimized by visual inspection. It was not possible to use acslX parameter estimation functions because RKDN2 and RLVER2 are array variables.

Figure 17 compares predicted and observed kidney/bone and liver/bone Pb ratios in adults. Standard deviations of observed means were not available for calculating residuals because they were calculated from group mean tissue concentration reported in Barry ([1975](#_ENREF_2)). Values for r2 for kidney/bone predictions (of average of male and female ratios) were 0.95 and 0.77 for AALM-LG and AALM-OF, respectively. Values for r2 for liver/bone predictions were 0.96 and 0.93 for AALM-LG and AALM-OF, respectively.

## 7.5 Optimization of Soft Tissue-to-Bone Pb Ratio

Two studies provide data to evaluate the relationship between plasma or serum blood Pb and bone Pb concentrations ([Cake et al. 1996](#_ENREF_8); [Hernández-Avila et al. 1998](#_ENREF_15)). Cake et al. ([1996](#_ENREF_8)) measured paired serum, tibia, and calcaneus Pb concentrations in 49 adult male Pb workers, and reported corresponding linear regression parameters. Hernandez-Avila et al. ([1998](#_ENREF_15)) measured paired plasma, tibia and patella Pb concentrations in 26 adults (20 female) who had no known occupational exposures to Pb. These data can be used to derive corresponding linear regression parameters for the log-transformed plasma Pb. Individual subject data were digitized from Figure 1 of Hernandez-Avila et al. ([1998](#_ENREF_15)), and linear regression parameters derived for the untransformed plasma Pb concentrations, in order to compare these with the linear regression parameters from Cake et al. ([1996](#_ENREF_8)).

Bone Pb/Plasma Pb slopes at age 50 years were predicted from AALM-LG and AALM-OF from a series of simulations in which Pb intake was varied from 1 to 1000 µg/day. Table 17 and Figure 18 compare predicted and observed slopes based on data from Cake et al. ([1996](#_ENREF_8)) and Hernandez-Avila et al. ([1998](#_ENREF_15)). Given the relatively low residuals for cortical bone, which were within the range -2 to 2, no further optimization for either model was needed for the respective parameters.

## 7.6 Optimization of Bone Pb Elimination Kinetics

Nilsson et al. ([1991](#_ENREF_34)) reported longitudinal data on blood and finger bone Pb concentrations in 14 Pb workers for period ranging from 8–18 years following cessation of their occupational exposures. The median blood Pb concentration at the end of exposure was approximately 45 µg/dL. The decline in bone Pb concentration was described by a first-order model with a single rate constant. Estimates of elimination half-times for each individual were reported. The group median was 16 years (95% CI: 12, 23), and the decline in blood Pb was described by a tri-exponential model with the following parameters.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameter** | **Unit** | **C1**  **(95% CI)** | **C2**  **(95% CI)** | **C3**  **(95% CI)** |
| t1/2 | year | 34 day  (29, 41) | 1.2 year  (0.85, 1.8) | 13 year  (10, 18) |
| C | µg/dL | 10.2 | 12.6 | 22.8 |

AALM-OF simulations were run for a constant Pb intake from birth to age 60 years, to achieve a terminal blood Pb concentration of approximately 45 µg/dL (1000 µg/day), followed by 20 years without exposure. A first-order exponential rate was estimated for the decline in cortical bone Pb concentrations predicted for 20 years following cessation of exposure. The AALM-OF parameter R0 (coefficient for Pb diffusion out of bone mineral into canalicules) was optimized (visual inspection) to achieve an elimination half-time from cortical cone of 16 years, the median value based on the Nilsson et al. ([1991](#_ENREF_34)) results.

AALM-LG simulations were run for a constant Pb intake from birth to age 60 years, to achieve a terminal blood Pb concentration of approximately 45 µg/dL (2000 µg/day), followed by 20 years without exposure. A first-order exponential rate was estimated for the decline in cortical bone Pb concentrations predicted for 20 years following cessation of exposure. The AALM-LG parameters FLONG (fraction of total transfer from the exchangeable bone directed to non-exchangeable bone) and RCORT (transfer rate from non-exchangeable cortical bone to diffusible plasma) were optimized (visual inspection) to achieve an elimination half-time from cortical bone of 16 years, the median value based on the Nilsson et al. ([1991](#_ENREF_34)) results. FLONG and RCORT are age-dependent arrays and were varied in the optimization by applying a constant (proportional) adjustment to all elements in the age array. The same adjustment factor was therefore applied to child and adult values, even though the optimization was made against data only for adults. The same adjustment factor was also applied to RTRAB (transfer rate from non-exchangeable cortical bone to diffusible plasma).

Figure 19 compares rates of elimination of Pb from bone and blood with the corresponding empirical models derived for Pb workers ([Nilsson et al. 1991](#_ENREF_34)). Elimination rates of Pb from bone predicted from the optimized models are within the 95% CI of the empirical model and yield residuals that range within the -2, 2, criteria (r2=0.99). Elimination half-times predicted for bone Pb (16 years) were identical to estimates from Nilsson et al. ([1991](#_ENREF_34)). Although elimination rates from blood predicted by the optimized models are approximately at the confidence limits of the empirical model, the initial model divergence is due largely to the slower (AALM-LG) or faster (AALM-OF) elimination kinetics during the first 5 years following cessation of exposure; after which the models converge on the empirical model (r2=0.96 AALM-LG; r2 =0.99 AALM-OF). Half-times predicted for the period 5 to 20 years after exposure were 1.25 years from AALM-LG and 1.06 years from AALM-OF, similar to values predicted for C2 (1.2 year) from Nilsson et al. ([1991](#_ENREF_34)).

## 7.7 Evaluation of Blood Pb Elimination Kinetics in Adults

Rabinowitz et al. ([1976](#_ENREF_46)) conducted a pharmacokinetics study in which four adults ingested daily doses of [207Pb] nitrate for periods up to 124 days. Concentrations of 207Pb in blood, urine, and feces were then monitored during and following cessation of exposure, and data on daily intakes and blood concentrations for each subject were reported. Absorption fractions for Pb were estimated for each individual based on mass balance in feces.

Figure 20 compares observed and predicted blood 207Pb concentrations for the optimized AALM-LG and AALM-OF. Gastrointestinal absorption fractions were set in both models to the estimates for each individual reported in Rabinowitz et al. ([1976](#_ENREF_46)). No other changes were made to parameter values. Although both models AALM-LG predict a rise and decline in blood Pb concentrations, AALM-LG predictions are closer to the observations. Values for r2 for AALM-LG predictions are 0.99, 0.98, 0.92, and 0.97 for Subjects A, B, D, and E, respectively. Values for r2 for AALM-OF predictions range from 0.08 (Subject E) to 0.24 (Subjects A, B, and D). AALM-OF predicts slower accrual and decline of blood Pb, and lower peak blood Pb concentrations.

## 7.8 Evaluation of Blood Pb Elimination Kinetics in Infants

Only two studies provide data on the relationships between Pb dose and blood Pb concentration in infants ([Ryu et al. 1983](#_ENREF_48); [Sherlock and Quinn 1986](#_ENREF_50)). In the Ryu et al. ([1983](#_ENREF_48)) study, blood Pb concentrations were monitored in 25 formula-fed infants. From birth to age 111 days, infants were fed formula (packaged in cartons) that had a Pb concentration of approximately 20 µg/L. From age 112 to 195 days, a subset of the infants (n=7) were switched to formula (packaged in cans) that had a Pb concentration of approximately 57 µg/L. Formula intakes were measured, and provided estimates of Pb intakes in each subject. Ryu et al. ([1983](#_ENREF_48)) reported a table of individual Pb intakes, and presented a figure illustrating group mean blood Pb concentrations at various ages (these data were digitized for use in this analysis). Standard errors (or deviations) of mean blood Pb concentrations were not reported; however, based on Sherlock and Quinn ([1986](#_ENREF_50), see below), standard errors may have been approximately 10% of the means. The parameter for maternal blood Pb concentration was set at 10 µg/dL, the reported maternal mean for the study. Lead absorption was not quantified in Ryu et al. ([1983](#_ENREF_48)); therefore, the gastrointestinal absorption fraction during infancy was set to 40%, based on estimates from mass balance studies ([Ziegler et al. 1978](#_ENREF_61)). No other changes were made to parameter values. Figure 21 compares predicted and observed blood Pb concentrations for the two exposure regimens (carton formula or carton followed by canned formula). Simulations are shown for the mean intake (12–20 µg/day) and ± 1 SD (10–18 µg/day, 15–22 µg/day). AALM-LG encompasses most of the observations within ±1 SD of the mean intakes. AALM-OF predictions are higher than observations. If standard errors of mean blood Pb concentrations were 10% of the mean, residuals for AALM-LG predictions ranged from -3.7 to 0.15 for carton exposures (mean -1.2). Residuals for AALM-OF predictions ranged from -3.0 to 4.4 (mean 2.0). Both models capture the increase in blood Pb concentration associated with the switch the higher Pb intakes for canned formula and the overall temporal trends in the observations; r2 for predictions were 0.85 and 0.76 for AALM-LG and AALM-OF, respectively.

Sherlock and Quinn ([1986](#_ENREF_50)) measured blood Pb concentration in 131 infants at age 13 weeks and estimated dietary intake of Pb for each infant based on Pb measurements made in duplicate diet samples collected daily during week 13. Sherlock and Quinn ([1986](#_ENREF_50)) reported a plot of blood Pb means and standard errors for group mean dietary Pb intakes (these data were digitized for use in this analysis). The parameter for maternal blood Pb concentration was set at 18 µg/dL, the reported maternal geometric mean. The gastrointestinal absorption fraction was set at 40% for infants; the same value used in simulations of Ryu et al. ([1983](#_ENREF_48)). Figure 22 compares predicted and observed blood Pb concentrations for the range of Pb intakes in the study. Both models reproduce the general shape of the observed curvilinear dose-blood Pb relationship; the apparent plateau observed at the higher end of the dose range, however, is achieved at higher doses in the models (>800 µg/day AALM-LG, >600 AALM-OF). Although the model results for the plateau contributed to high residuals at the highest Pb intake (>200 µg/day), residuals for lower Pb doses ranged from -4.8 to 1.5 (mean -2.3) for AALM-LG and -4.3 to 2.2 (mean – 1.0) for AALM-OF. The overall dynamics of increasing blood Pb with increasing Pb dose was predicted with r2 =0.95 for AALM-LG and 0.98 for AALM-OF. One possible explanation for the higher plateaus in the dose-blood Pb relationship predicted from both models is that the models may estimate higher saturation levels of Pb in red blood cells than actually occurred in the infants in the Sherlock and Quinn ([1986](#_ENREF_50)) study. Parameter values for red blood cell uptake are based on data collected on adults, and have not been optimized for infants due to an absence of good supporting data (see Section 7.2).

# 8.0 CONCLUSIONS AND IMPLICATIONS OF PERFORMANCE OF OPTIMIZED MODELS

The initial configuration of the AALM biokinetics model was an acslX implementation of the Leggett ([1993](#_ENREF_27)) and O’Flaherty ([1993](#_ENREF_38), [1995](#_ENREF_39)) models. The current version of the AALM has introduced several changes to both models, including new parameters (see Table 19), and has optimized parameter values against the same data sets. Some of the data used in the optimization were not available at the time the original models were developed. Optimization against a common set of data resulted in convergence of model predictions for blood, bone, and soft tissue (see Figures 23 and 24). The optimized AALM-LG and AALM-OF predict similar blood, bone, and soft tissue Pb concentration (see Table 20). Evaluation of model predictions of blood Pb relationships at known ingestion doses of Pb was limited to data in a few adult subjects ([Rabinowitz et al. 1976](#_ENREF_46)), and only two studies in infants (where Pb ingestion doses were estimated from dietary [formula] Pb measurements) ([Ryu et al. 1983](#_ENREF_48); [Sherlock and Quinn 1986](#_ENREF_50)). No data were available on blood Pb concentrations in children or adolescents, for whom Pb ingestion doses were known with certainty. Several studies have reconstructed Pb intakes in children from exposure models supported by measurements of environmental exposure concentrations ([Bornschein et al. 1985](#_ENREF_7); [Dixon et al. 2009](#_ENREF_12); [Hogan et al. 1998](#_ENREF_16); [Lanphear and Roghmann 1997](#_ENREF_22); [Lanphear et al. 1998](#_ENREF_23); [Malcoe et al. 2002](#_ENREF_30); TerraGraphics [2004](#_ENREF_55)). However, these studies were not considered for evaluation of the AALM biokinetics models since they would introduce exposure uncertainty into the evaluation.

Although limited in scope, these evaluations provide several insights into model performance. In general, the AALM, in both AALM-LG and AALM-OF configurations, predicted observed blood Pb dynamics in infants and adults, in response to changing Pb dosing (see Figures 20–22). In infants, observed blood Pb concentrations were on average within ± 2 SE of the observed mean (mean residual range -2, 2). AALM-LG and AALM-OF predict similar quasi-steady state blood Pb concentrations in infants (Figures 21 and 22). Both models predict a higher plateau for the dose-blood Pb relationship than was observed in infants, however, this difference would be of quantitative significance only at intakes resulting in blood Pb concentrations >30 µg/dL.

AALM-OF predicts slower than observed blood Pb kinetics in adults compared to AALM-LG. This resulted in larger differences between predicted and observed blood Pb concentrations in controlled, short-term, exposure studies. More rapid blood Pb kinetics predicted by AALM-LG provided a closer agreement to observations (see Figure 20). Although short-term exposure studies revealed important differences in blood Pb kinetics predicted by AALM-LG and AALM-OF, both models predict well the long-term elimination rates of Pb from bone following decades of exposure, and its effect on long-term elimination of Pb from blood, that have been observed in worker populations following cessation of exposure (see Figure 19).

Optimization exercises also revealed differences in model structure that are relevant to model applications. Attempts to optimize AALM soft tissue/bone lead ratios solely by adjusting tissue/plasma partition coefficients were unsuccessful. Improved performance was achieved by introducing age-dependence and larger values for partition coefficients. O’Flaherty ([1993](#_ENREF_38), [1995](#_ENREF_39)) assigned values of 50 to the kidney/plasma and liver/plasma partition coefficients. The optimized values are substantially higher; approximately 1350 for plasma/kidney, and 1600 for plasma/liver, in infants that progressively decrease with age to adult values of approximately 700 and 800 respectively. It is possible, and likely, that these large adjustments were necessary because the assumption of flow-limited transfer of Pb into and out of soft tissue Pb does not accurately reflect the complexities of age-dependent transport and retention of Pb in soft tissues. In support of this hypothesis, optimization of the bidirectional transfer coefficients that govern uptake and retention of Pb in kidney and liver successfully predicted observations made in infants, children and adults (see Figure 17).

AALM-LG and AALM-OF were also successfully optimized to predict observed relationships between plasma and whole blood Pb concentrations in adults even though the two models use very different mathematical approaches to simulating uptake and retention of Pb in red blood cells. AALM-OF simulates binding of Pb with red blood cells as a saturable instantaneous equilibrium. AALM-LG simulates bidirectional transfer between plasma and red blood cells, with saturable transfer into red blood cells. Transfer out of red blood cells in AALM-LG is age-dependent and faster in children than in adults. The validity of the age-dependence was not rigorously explored in this analysis. What little data there are on plasma-red blood cell relationships in children does not suggest an appreciable difference in the relationship for children and adults ([Bergdahl et al. 1999](#_ENREF_6)). Since the age-dependence assumption could not be rigorously evaluated it is retained in AALM-LG.

The most substantial differences in the structures of AALM-LG and AALM-OF are in the simulation of bone Pb kinetics. In AALM-LG, bone Pb kinetics are represented as age-dependent rate coefficients for transfer of Pb into and out of bone. In AALM-OF, bone Pb kinetics are simulated as outcomes of a physiological model of bone formation and resorption. The physiological approach to bone metabolism implemented in AALM-OF allows the model to be used to explore relationships between bone metabolism and Pb kinetics. This is potentially useful for simulating Pb kinetics in various bone metabolism contexts associated with life stages (e.g., pregnancy, menopause; [O’Flaherty 2000](#_ENREF_42)), diseases (e.g., bone wasting diseases), and environments (e.g., weightlessness).

Although, at this time, the AALM remains a research model requiring further external review, it possesses several attributes (discussed in the following bullets) that make it attractive in human health risk assessment when estimating Pb internal dosimetry following real or hypothetical environmental exposures.

* Currently, human health risk assessment of Pb is conducted using two separate regulatory models, the IEUBK model for Lead in Children and Adult Lead Methodology. The IEUBK model has a terminal age of 7 years. The Adult Lead Methodology is limited to adults. The AALM provides a single physiological/compartmental model capable of predicting blood Pb concentrations at all ages from birth through adulthood. The AALM would replace or supplement the results of the two separate models, and would provide additional assessment capability for older children and adolescent subpopulations.
* The current regulatory model, the Adult Lead Methodology is a slope factor model in which biokinetics are represented as a single variable relating the linear slope of the change in blood Pb concentration per unit change of absorbed Pb (µg/day). The AALM offers a more mechanistic approach to simulating Pb kinetics that can incorporate information on age, growth, life stage, and other physiological variables that may affect Pb kinetics.
* The AALM can simulate exposures in time steps as small as a single day. This allows predictions of blood Pb concentrations associated with acute or highly intermittent exposures. The IEUBK model and Adult Lead Methodology simulate quasi-steady state blood Pb concentration associated with exposures that have durations of >3 months. Shorter-term dynamics of blood Pb concentrations expected to occur with exposures that vary over days or weeks cannot be simulated with the IEUBK model or the ALM.
* The AALM can predict concentrations of Pb in bone. This offers the potential for using estimates of bone Pb as an internal dosimeter in assessing health risk from exposure to environmental Pb. Bone Pb may be more suitable than blood Pb when predicting risk for certain effects of Pb such as hypertension (U.S. EPA [2013](#_ENREF_58)).
* The respiratory tract model in the AALM provides a more realistic simulation of inhaled aerosols of Pb that incorporates information on air Pb concentrations, air Pb particle size, solubility, receptor activity levels (which determine inhalation volumes), and age. This capability of the AALM is a major improvement over the respiratory tract representation in the IEUBK model, which consists only of parameters for inhalation volumes, and a single parameter for the absorption fraction of inhaled Pb (from the lung and GI-tract). The Adult Lead Methodology does not represent the respiratory tract.

# 9.0 CALIBRATING THE AALM TO THE IEUBK MODEL

Figure 25 compares predictions of the AALM and the IEUBK model for a continuous dust Pb intake of 10 µg/day. In both models, the relative bioavailability (RBA) for Pb in dust was assumed to be 60%. This corresponds to an absolute bioavailability of approximately 20% at age 2 years in the AALM and 30% in the IEUBK model. At age 2-3 years the IEUBK model predicts a blood Pb concentration of 1.1 µg/dL; AALM-LG and AALM-OF predict 2.1 and 2.8 µg/dL, respectively.

Table 21 compares predictions of adult blood Pb concentrations from the Adult Lead Methodology and AALM, for an exposure to 1000 ppm. In both models, the RBA for Pb in dust was assumed to be 60%. This corresponds to an absolute bioavailability of approximately 4.8% in the AALM and 12% in the Adult Lead Methodology. The Adult Lead Methodology predicts a blood Pb concentration of 2.9 µg/dL; AALM-LG and AALM-OF predict 3.1 and 4.6 µg/dL at age 30 years (mid-point for age range in the Adult Lead Methodology, 17-45 years), respectively.

The optimized AALM discussed in Section 7 thus predicts blood Pb concentrations in children that are approximately 2-fold higher than the currently established regulatory IEUBK model based on the same Pb intakes. Data available for optimizing and evaluating performance of the Pb biokinetics models are largely limited to data for Pb kinetics in adults. Only two studies have reported data on intake-blood Pb relationships in infants ([Ryu et al. 1983](#_ENREF_48); [Sherlock and Quinn 1986](#_ENREF_50)), and no data of this type are available for children in the age range 1-7 years, the age range simulated in the IEUBK model. Given the large uncertainties in the available data on intake-blood Pb relationships in children, the model differences in absolute terms are relatively small in the context of model capabilities (e.g., approximately 1 - 2 µg/dL in children for a dust Pb ingestion rate of 10 µg/day). These small differences in model estimates, however, could have disproportionate costs implications to consider in making risk management decisions at contaminate sites, which are typically based on a “not-to-exceed” blood Pb concentration (U.S. EPA [1994](#_ENREF_57)).

The IEUBK model has a long, established history of use in risk assessment and support for soil clean-up goals at hazardous waste sites. Thus, it was deemed worthwhile to further evaluate the most sensitive AALM parameter values to determine which parameters values could be calibrated against the IEUBK model output for child blood Pb concentrations relative to Pb intake without altering the AALM model performance in simulating the infant and adult data.

This additional evaluation identified value changes for a single biokinetic parameter, *RRBC*, that were sufficient to align the AALM-LG results more closely with the IEUBK model results. The RRBC parameter controls the rate of return of Pb from red blood cells to plasma. Support for adjusting this parameter is based on the following three arguments: (1) sensitivity analyses of the AALM-LG revealed that blood Pb predictions were highly sensitive to parameters controlling plasma-RBC Pb exchange rates (Section 5, Table 4), (2) the parameter *RRBC* value is derived from an age-dependent array that allows adjustment of the parameter value for children without altering values for infants or adults, precluding degradation of model performance in estimating Pb kinetics for infant and adult subpopulations; and (3) the RRBC parameter value for children remains uncertain and has no data support, however the upward adjustment needed for this parameter (i.e., faster outflow from red blood cells) is consistent with assumptions that were made in the early development of the Leggett model, namely that removal half-times of Pb from red blood cells are expected to be shorter in young children than in adults (Leggett, 1993). The *RRBC* parameter was adjusted upward until close agreement was achieved between blood Pb predicted by AALM-LG and the IEUBK model for a constant ingestion intake of 10 µg/day Pb in surface dust, and an RBA relative to soluble Pb=0.60 (compare Figure 25 with 26).

Using the same rationale, red cell parameters in AALM-OF were adjusted to align the AALM-OF blood Pb predictions in children more closely with the IEUBK model results. Unlike the AALM-LG, which represents Pb exchanges between plasma and red blood cell with first order rate coefficients, the AALM-OF represents binding of Pb in red blood cells as an instantaneous binding equilibrium with plasma Pb controlled by two parameters, a half saturation parameter (*KBIND*) and maximum binding capacity (*BIND*), both of which are constants and independent of age. Although, either of the two parameters could be adjusted, the half saturation parameter (*KBIND*) was selected in order to keep the binding capacity unchanged, which is similar to the strategy used in resolving differences with AALM-LG.

As illustrated in Figure 26, adjustments to the RBC parameters in the AALM-LG and AALM-OF resulted in close agreement with child blood Pb profiles in children predicted by the IEUBK model. At age 2-3 years the IEUBK model predicts a blood Pb concentration of 1.1 µg/dL; AALM-LG and AALM-OF predict 1.3 and 1.5 µg/dL, respectively, for a dust Pb intake of 10 µg/dL. Because the parameter adjustments were age-dependent and were restricted to children, the adjustments had no effect on predictions of Pb kinetics in adults, and the revised AALM models performed similarly to the optimized version in predicting observed Pb kinetics in adults. Similarly, the adjustments made to the AALM RBC parameter values for the children subpopulation had minimal effect on the model predictions of blood Pb levels or kinetics in infants (see Figures 27 and 28). Blood and tissue Pb concentrations predicted by the revised AALM are presented in Table 22.

# 10. 0 DATA NEEDS AND FURTHER EVALUATION OF THE AALM

The improvements in the AALM discussed in this report demonstrate the considerable advancements made in the AALM model capability and exposure interface, as well as the optimized parameters that control important model predictions (e.g., plasma/RBC ratios, soft tissue/bone ratios, plasma-to-urine clearance), and that have been optimized against the available data in infants and adults.

Of particular interest to risk assessment applications are predictions of blood and bone Pb, as these two biomarkers have been used extensively to establish dose-response relationships for health effects of Pb in humans (U.S. EPA [2013](#_ENREF_58)). The two models predict long-term accrual of Pb in blood and bone Pb levels in adults (ages >16), that differ by less than 20%. This agreement is remarkable, given the very different approaches used to simulate bone Pb, which is the major depot for Pb in the body. This magnitude of difference is less than observed inter-individual variability in blood and bone Pb measurements in humans (CDC [2013](#_ENREF_9); [Hu et al. 2007](#_ENREF_17); U.S. EPA [2013](#_ENREF_58)). The two models also predict similar blood Pb concentrations in children. At an earlier age of 2 years, however, blood Pb concentrations predicted from AALM-LG are approximately 25% lower than predictions from AALM-OF, however, data are limited, and additional data are likely to result in improvements in model performance.

Blood Pb concentrations in adults predicted from the AALM are very similar to predictions from the Adult Lead Methodology for the same soil Pb concentrations. Predictions for infants are similar between the AALM and the IEUBK. With the adjusted RBC parameter value, the AALM and IEUBK model predict similar blood Pb concentrations in children for the same dust Pb intakes and RBA assumptions. Subject to further external peer review and verification of the AALM results, the agreement between the AALM, the IEUBK model, and the ALM supports the potential future use of the AALM in risk assessment applications to supplement or replace the IEUBK model and the ALM in supporting regulatory decisions. At present, however, the IEUBK model and the ALM remain the established methods that will be used for regulatory decisions.

Recommendations for data to reduce uncertainty in the AALM model results, and improve the consistency among all model predictions include the following:

* *Resolve differences between the AALM-LG and AALM-OF predictions of blood Pb kinetics.* AALM-OF predicts slower accrual and elimination of Pb from blood compared to AALM-LG, while AALM-LG more close reproduced blood Pb kinetics observed in the short-term Pb dosing studies of Rabinowitz et al. ([1976](#_ENREF_46)). Additional data on blood Pb kinetics may serve to improve the optimization of both models, and resolve these differences. This will be important for application of either model to simulating blood Pb dynamics associated with short-term or highly variable exposures.
* *Evaluate and optimize AALM-OF bone metabolism parameters.* A literature search and review of newer data on rates of bone production and resorption may provide a basis for re-optimization of AALM-OF or its extension to include simulations of specific bone metabolism scenarios of interest to toxicology or risk assessment (e.g., pregnancy, osteomalacia).
* *Further verify AALM-LG and AALM-OF predictions.* Additional observations in humans should be identified that can serve to evaluate the performance of the optimized AALM (and that were not used in the optimization). Ideally, these would be blood and/or bone Pb measurements in people for whom Pb intakes are known with reasonable certainty. Ethical concerns typically preclude Pb dosing experiments; therefore, Pb doses must be estimated with accurate tools such as duplicate diet surveys or dietary recalls and information on Pb levels in diet and other relevant exposure media. Types of data that would be valuable for model validation include: (1) blood soft tissue or bone Pb levels in children or adults for whom Pb dosage is known or can be reliable estimated from exposure data; (2) changes in blood, soft tissue or bone Pb levels in children or adults following and abrupt change (increase or decrease) in Pb exposure; (3) steady state (or quasi-steady state) blood/soft tissue blood/bone Pb ratios in children or adults; (4) urinary Pb clearance from blood or plasma in children or adults; and (5) plasma/whole blood concentration ratios in children.
* *Evaluate and document the empirical basis for exposure model parameters.* Most of the exposure parameter values currently in the AALM serve as placeholders and should, in the future, be replaced with default values for specific receptor populations for which an empirical basis can be provided.
* *Further refine the respiratory tract model*. The current version of the AALM includes values for inhalation rates and deposition fractions for the general public, as defined by ICRP ([2000](#_ENREF_21)). These values do not adequately represent many receptor populations of interest who have activity levels that differ from general population assumptions (e.g., workers). Additional parameter value matrices should be developed to represent selected receptor populations of interest.

Finally, the AALM has been developed with a relatively easy to use and versatile exposure interface, access to model parameters and values, and transparency of model code to support stakeholder use and evaluation internally and external to the Agency. It is recommendation of this report that the AALM be made available to the Agency and the research community as a beta test version to facilitate additional case studies, parameter refinements and external evaluation; and to advance the model towards regulatory use and exposure assessment.

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1. This approach to sensitivity analysis does not consider potential interactions between parameters. Sensitivity coefficients measured in univariate analyses may be larger or smaller than SSCs measured in multivariate analyses (i.e., when multiple parameters are varied simultaneously). [↑](#footnote-ref-1)